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EP 0 371 438 A2

(54) 3,5-Di-tertiary-butyl-4-hydroxyphenyl-1,3,4-thiadiazoles, and oxadiazoles and 3,5-di-tertiary-butyl-4-hydroxyphenyl-1,2,4-thiadazoles, oxadiazoles and triazoles as antiinflammatory agents.

(57) The present invention is novel compounds which are 3,5-di-tertiary-butyl-4-hydroxyphenyl substituted 1,2,4- and 1,3,4-thiadazoles and oxadiazoles, and 1,2,4-triazoles, and pharmaceutically acceptable additions and base salts thereof, pharmaceutical compositions and methods of use therefor. The invention compounds are now found to have activity as inhibitors of 5-lipoxygenase and/or cyclooxygenase providing treatment of conditions advantage usly affected by such inhibition including inflammation, arthritis, pain, fever, and the lik .

3,5-DI-TERTIARY-BUTYL-4-HYDROXYPHENYL-1,3,4-THIADIAZOLES, AND OXADIAZOLES AND 3,5-DI-TERTIARY-BUTYL-4-HYDROXYPHENYL-1,2,4-THIADAZOLES, OXADIAZOLES AND TRIAZOLES AS ANTIINFLAMMATORY AGENTS

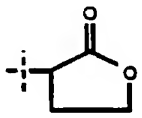
BACKGROUND OF THE INVENTION

The present invention is novel compounds which are 3,5-di-tertiary-butyl-4-hydroxyphenyl substituted 1,2,4- and 1,3,4-thiadazoles and oxadiazoles, and 1,2,4-triazoles, and pharmaceutically acceptable acid addition or base salts thereof, pharmaceutical compositions and methods of use therefor. The invention compounds are now found to have activity as inhibitors of 5-lipoxygenase and/or cyclooxygenase providing treatment of conditions advantageously affected by such inhibition including inflammation, arthritis, pain, pyrrhia, and the like. Thus, the present invention is also a pharmaceutical composition or method of use therefor.

U.S. Patent No. 4,618,617 includes a generic disclosure for 1,2,4-oxadiazole derivatives of groups which may be read to include 3,5-di-tertiary butyl-4-hydroxy phenyl substituents. However, none of the disclosure specifically shows the unexpected activity of combined ring systems of the present oxadiazole and 3,5-ditertiary-butyl-4-hydroxyphenyl groups. Similarly, J61005-072-A of Derwent Abstract No. 86-051943/08 does not recognize the advantages of the present ring combination.

3,5-di-tertiary-butyl-4-hydroxyphenyl substituents are also shown on pyrrole ring-containing compounds in European Application No. 269,981 abstracted as Derwent Abstract No. 88-15622/423, showing usefulness as analgesic, antipyretic, antiinflammatory, and antipsoriatic agents, and for treating bone disorders.

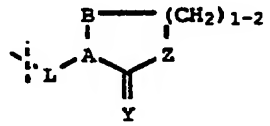
A 3,5-di-tertiarybutyl-4-substituted benzylidene on a



ring is disclosed for use as antiinflammatory, analgesic, antipyretic, and antiplatelet aggregation agents in an abstract of Japanese Application 88024498 in the Derwent Alerting Bulletin J8-B, Vol. 88, No. 21 by Kanegafuchi Kagaku.

A 3,5-di-tertiarybutyl-4-hydroxybenzyl substituent for 2-pyrrolidone derivatives as antiinflammatory, analgesic, and antipyretic agents is taught by Japanese Application No. J63119-461 and J63115-859 in Derwent Abstract No. 88-180570/26 and 88-178973/26, respectively, by Eisai KK.

Other compounds disclosing either specifically or generically 3,5-di-tertiarybutyl-4-hydroxy substituents include compounds that are, for example, 3-ethenylpyridines, in US 4,743,606 abstracted in Derwent Abstract No. 88-147234/21 and



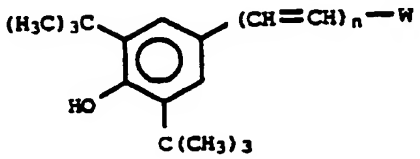
wherein L is lower alkylene, sulphur or sulphinyl; and Y is alkoxyimino, or oxo; A-B- is CH-CH_2- or C=CH-; and Z is lower alkylene or sulphur; in Japanese Application No. J62,081,343 in Derwent Abstract 87-140934/20.

Also, thiazolidinone derivatives are shown in European Application No. 211670 by Eli Lilly and Co. of Derwent Abstract No. 87-051809/08 and thiazole derivatives in Japanese Application No. 62132871 by Yamanouchi Pharm KK discussed in Derwent Abstract No. 87-203585/29. In the Lilly disclosure the ring systems were linked by a saturated carbon group.

Thus, the differ nces between the present invention and the teachings of the references are readily apparent.

SUMMARY OF THE INVENTION

The present invention is a compound of the formula (I)

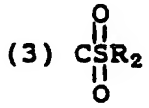


I

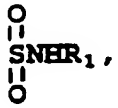
and a pharmaceutically acceptable acid addition or base salt thereof and hydrates; wherein n is zero or one, and W is

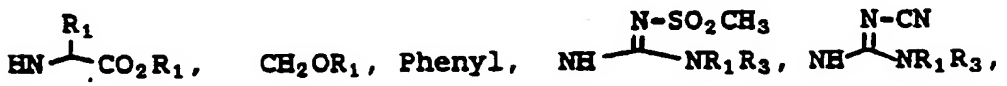
wherein X is N, NR_1, O, or S wherein R_1 is hydrogen or lower alkyl;
Z is O, S, NR_1 or N wherein R_1 is independently as defined above; with the proviso that when Z is NR_1 or N at the same time that X is N or NR_1 then X must be N when Z is NR_1 and X must be NR_1 when Z is N and also with the proviso that when X is S or O then Z must be N, and that when Z is S or O then X must be N, i.e. one of either X or Z must be N;
Y is (1) C-SR_1 wherein R_1 is independently as defined above,

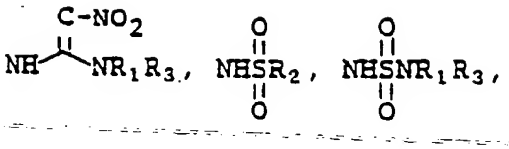
(2) C-$\overset{O}{\overset{\|}{S}}R_2$ wherein R_2 is lower alkyl,



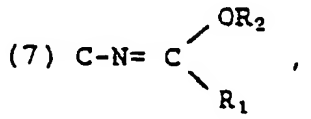
wherein R_2 is as defined above, (4) C-NR_1R_3 wherein R_1 is independently as defined above and R_3 is hydrogen or lower alkyl, (5) COR_1 wherein R_1 is independently as defined above, (6) CR_4 wherein R_4 is halogen, CF_3, CO_2R_1, or







NR_1OR_3, $S(CH_2)_mCO_2H$, CN, H, alkyl, $NH(CH_2)_mOH$, CCl_3, $CONR_1R_3$, $CSNR_1R_3$, CH_2X_{10}, $CH_2NR_{11}R_{13}$, $NHCSNHCO_2R_2$, CH_2SR_2, $CH_2SO_2R_2$, or $NHNH_2$



wherein m is 1, 2, or 3; R_{11} and R_{13} are hydrogen, lower alkyl or taken together with N form a saturated ring having from 4 to 6 carbons; X_{10} is halogen or NO_2; R_5 is H, lower alkyl or OR_1 and R_1, R_2, and R_3 are independently as defined above.

The present invention is also a pharmaceutical composition for the treatment of conditions advantageously affected by the inhibition of 5-lipoxygenase and/or cyclooxygenase which comprises an amount effective for the treatment of the condition of a compound of the formula I and the pharmaceutically acceptable acid addition or base salt thereof together with a pharmaceutically acceptable carrier. The condition is meant to include, for example, arthritis or other inflammtory diseases, allergic diseases, pain, fever, and psoriasis, but preferably inflammatory diseases.

The present invention is also a method of use of a compound of formula I or salts thereof for the manufacturing of pharmaceuticals for treatment of the condition as noted above in a mammal, including humans, suffering therefrom.

Pharmaceutical composition or use of the compound or salt of formula I is meant to include treatment understood to be prophylactic pertinent to the foregoing named condition.

The preferred compounds of the formula I in the present invention include:
5-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-thiadiazole-2(3H)-thione,
5-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-oxadiazol-2(3H)-one,
5-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-oxadiazole-2(3H)-thione,
5-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethenyl]-1,3,4-oxadiazole-2(3H)-one,
2,4-Dihydro-5-[2-[4-hydroxy-3,5-bis(1,1-dimethylethyl)phenyl]ethenyl]-3H-1,2,4-triazole-3-thione,
5-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2,4-dihydro-3H-1,2,4-triazol-3-one,
5-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2,4-dihydro-4-methyl-3H-1,2,4-triazol-3-one,
5-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethenyl]-2,4-dihydro-3H-1,2,4-triazol-3-one,
5-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2,4-dihydro-3H-1,2,4-triazole-3-thione, and
5-[2-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethenyl]-1,3,4-oxadiazole-2(3H)-thione.
4-(5-amino-1,3,4-thiadiazol-2-yl)-2,6-bis(1,1-dimethylethyl)phenol,
N-[5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-thiadiazol-2-yl]guanidine and the monohydrochloride salt thereof, and
5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-thiadiazol-2-yl]cyanamide, and the 2-hydroxy-N,N,N-trimethylethanaminum salt thereof.

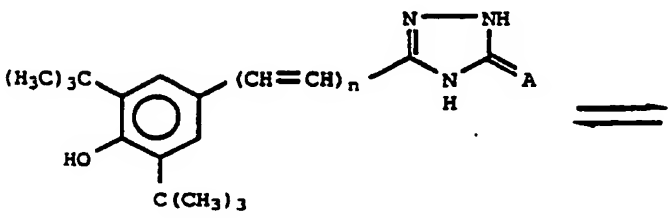
Of these the most preferred are:
5-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-thiadiazole-2(3H)-thione,
4-(5-Amino-1,3,4-thiadiazol-2-yl)-2,6-bis(1,1-dimethylethyl)phenol,
N-[5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-thiadiazol-2-yl]guanidine and the monohydrochloride salt thereof, and
5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-thiadiazol-2-yl]cyanamide, and the 2-hydroxy-N,N,N-trimethylethanaminum salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

In the compounds of formula (I) the term "lower alkyl" includes an alkyl group of from one to six carbons such as methyl, ethyl, propyl, butyl, and the lik and isom rs thereof. Halogen is chloro, bromo or

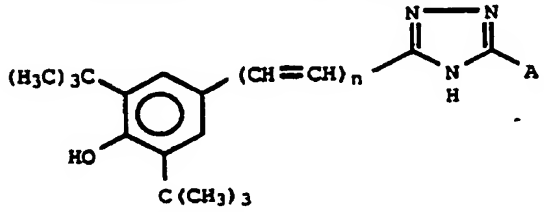
fluoro.

Th compounds I of th invention may exist as tautomers which are readily determin d from art recognized tautomerism. Such tautomers are, for example, represented by formula I′ and II″ as follows:



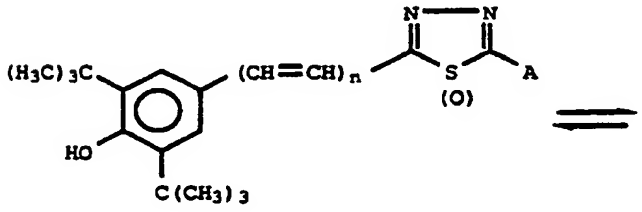
I′

wherein A is O, NH or S



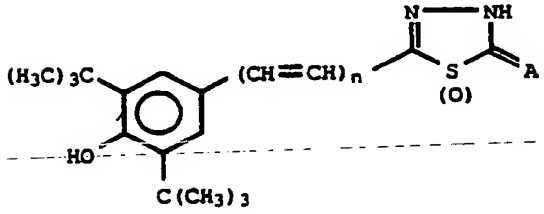
wherein A is OH, NH_2 or SH

or



II″

wherein A is OH, NH_2 or SH



wherein A is O, NH, or S.

Appropriate compounds of formula (I) are useful in the free base form, in the form of base salts where possible, and in the form of acid addition salts. The three forms are within the scope of the invention. In practice, use of the salt form amounts to use of the base form. Pharmaceutically acceptable salts within the scope of the invention may be those derived from mineral acids such as hydrochloric acid and sulfuric acid; and organic acids such as ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and the like, giving the hydrochloride, sulfamate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and the like, respectively, or those derived from bases such as suitable organic and inorganic bases. Examples of

pharmaceutically acceptabl base addition salts with compounds of the present invention include organic bases which are nontoxic and strong enough to form such salts. These organic bases form a class whose limits are readily understood by those skilled in the art. Merely for purposes of illustration, the class may be said to include mono-, di-, and trialkylamines such as methylamine, dimethylamine, and triethylamine; mono-, di-, or trihydroxyalkylamines such as mono-, di-, or triethanolamine; amino acids such as arginine and lysine; guanidine; choline N-methylglucosamine; N-methylglucamine; L-glutamine; N-methylpiperazine; morpholine; ethylenediamine; N-benzylphenethylamine; tris(hydroxymethyl)aminomethane; and the like. (See for example, "Pharmaceutical Salts," J. Pharm. Sci., 66(1):1-19 (1977).) Salts of inorganic bases include sodium, potassium, calcium or the like.

The acid addition salts of said basic compounds are prepared either by dissolving the free base or acid of compound I in aqueous or aqueous alcohol solution or other suitable solvents containing the appropriate acid or base and isolating the salt by evaporating the solution, or by reacting the free base of compound I with an acid as well as reacting compound I having an acid group thereon with a base such that the reactions are in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution. Salts can also be prepared by adding base to an aqueous alcohol solution of another salt.

The compounds of the invention may contain geometric isomers. Thus, the invention includes the individual isomers and mixtures thereof. The individual isomers may be prepared or isolated by methods known in the art.

In determining when a lipoxygenase, cyclooxygenase, or dual lipoxygenase/cyclooxygenase inhibitor is indicated, of course inter alia, the particular condition in question and its severity, as well as the age, sex, weight, and the like of the subject to be treated, must be taken into consideration and this determination is within the skill of the attendant physician.

For medical use, the amount required of a compound of formula (I) or pharmacologically acceptable salt thereof to achieve a therapeutic effect will, of course, vary both with the particular compound, the route of administration, the mammal under treatment, and the particular disorder or disease concerned. A suitable dose of a compound of formula (I) or pharmacologically acceptable salt thereof for a mammal suffering from, or likely to suffer from any condition as described hereinbefore is 0.1 µg-500 mg of the compound per kilogram body weight. In the case of systemic administration, the dose may be in the range of 0.5 to 500 mg of the compound per kilogram body weight, the most preferred dosage being 0.5 to 50 mg/kg of mammal body weight administered two or three times daily. In the case of topical administration, e.g., to the skin or eye, a suitable dose may be in the range 0.1 ng-100 µg of the compound per kilogram, typically about 0.1 µg/kg.

In the case of oral dosing for the treatment or prophylaxis of arthritis or inflammation in general, due to any course, a suitable dose of a compound of formula (I) or physiologically acceptable salt thereof, may be as specified in the preceding paragraph, but most preferably is from 1 mg to 10 mg of the compound per kilogram, the most preferred dosage being from 1 mg to 5 mg/kg of mammal body weight, for example from 1 to 2 mg/kg.

It is understood that the ordinarily skilled physician or veterinarian will readily determine and prescribe the effective amount of the compound to prevent or arrest the progress of the condition for which treatment is administered. In so proceeding, the physician or veterinarian could employ relatively low doses at first, subsequently increasing the dose until a maximum response is obtained.

While it is possible for an active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation comprising a compound of formula (I) or a pharmacologically acceptable acid addition or base salt thereof and a pharmacologically acceptable carrier therefor. Such formulations constitute a further feature of the present invention.

The formulations, both for veterinary and for human medical use, of the present invention comprise an active ingredient in association with a pharmaceutically acceptable carrier therefor and optionally other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

The formulations include those in a form suitable for oral, pulmonary, ophthalmic, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), intraarticular, topical, nasal, or buccal administration. Such formulations are understood to include long-acting formulations known in the art.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well-known in th art of pharmacy. All methods may include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into th

desired formulation.

Formulations of th pr s nt invention suitable for oral administration may be in th form of discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the activ ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or nonaqueous liquid; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. The active ingredient may also be in the form of a bolus, electuary, or paste.

The usefulness of the compounds of the present invention as inhibitors of the 5-lipoxygenase enzyme, cyclooxygenase, or in treating related diseases or conditions may be demonstrated by their effectiveness in various standard test procedures. A description of each procedure follows.

ARBL/ARBC Whole Cell 5-Lipoxygenase and Cyclooxygenase Assays

Materials

The rat basophilic leukemia cell line (RBL-1) was obtained from the American Type Culture Collection (Rockville, MD).

Radioimmunoassay (RIA) kits of LTB_4 and $PGF_{2\alpha}$ were obtained from Amersham (Arlington Heights, IL) and Seragen (Boston, MA), respectively.

All tissue culture media were obtained from GIBCO (Grand Island, NY).

Method

RBL-1 cells are grown in suspension culture in Eagle's minimum essential medium supplemented with 12% fetal bovine serum at 37° C in an incubator supplied with air-5% carbon dioxide. Cells are harvested by centrifugation. They are washed with cold phosphate buffered saline pH 7.4 (PBS; NaCl, 7.1 g; Na_2HPO_4, 1.15 g; KH_2PO_4, 0.2 g; and KCl, 0.2 g/l). Cells are finally suspended in PBS containing 1.0 mM calcium at a density of $2x10^6$ cells/ml. Cells are incubated with and without test agent (in DMSO) (1% DMSO is without effect on arachidonic acid metabolism) for ten minutes at room temperature. Calcium ionophore A23187 (5 μM) is added and cells are incubated for seven minutes at 37° C. The reaction is stopped by chilling the tubes on ice for ten minutes. Cells are separated by centrifugation and the supernatant is stored at -20°. Aliquots (100 μl) are analyzed for LTB_4 and $PGF_{2\alpha}$ using radioimmunoassay kits as provided by the supplier.

Table 1 contains biochemical data obtained from this whole cell assay as IC_{50}s which are calculated as the amount of test compound causing 50% inhibition of LTB_4 or $PGF_{2\alpha}$ formation.

Table 1

	ARBL	ARBC
Example	IC_{50}[b] (μM)	IC_{50}[c] (μM)
4	5.7	0.86
8	10	8
7	1.4	2.5
15	4.5	2.5
17	1.6	
10	1.4	0.13

[b] IC_{50} for LTB_4 inhibition.
[c] IC_{50} for $PGF_{2\alpha}$ inhibition.

Carrageenan-Induced Rat Foot Paw Edema-2 (CFE-2) Assay: Protocol

Carrageenan solution (1% w/v) is prepared by dissolving 100 mg carrageenan (Marine Colloidal Div., Springfield, NJ) in 10 ml of steriie saiine (0.9%) solution (Travenol). The solution is vortexed for 30 to 45 minutes. Animals are dosed with compound one hour before carrageenan challenge. Foot paw edema is induced by injecting 0.10 ml of the 1% carrageenan subcutaneously into the plantar portion of the right hind paw of each rat under light anesthesia. Initial foot paw volume is measured immediately following carrageenan challenge using mercury plethysmography (Buxco Electronics). Edema is measured five hours after carrageenan. The difference between the five-hour and the initial paw volume is expressed as delta edema. The delta edema for each test group of animals is used to calculate the percent inhibition of edema achieved by the compound at the test dose compared with the vehicle control group. The ID_{40} (the dose at which swelling is inhibited by 40%) is calculated by probit analysis for the dose at which percent inhibition occurs.

Mycobacterium - Induced Rat Footpad Edema Assay (MFE): Protocol

Mycobacterium butyricum (5 mg/ml) is suspended in paraffin oil by sonication for ten minutes in an ice bath. Footpad edema is induced on Day 0 by injecting 0.1 ml of the Mycobacterium mixture into the left hindpaw of lightly anesthetized rats. Swelling in the injected hindpaw is determined by mercury plethysmography 72 hours after injection. Groups of rats are treated with test compounds (suspended in 0.5% hydroxypropyl methylcellulose with 0.2% Tween-80) or vehicle one hour before Mycobacterium injection and on Days 1 and 2. Inhibition of swelling is determined by comparing the change in hindpaw volume in compound-and vehicle-treated rats. An ID_{40} (the dose at which swelling is inhibited by 40%) is calculated by probit analysis.

Gastric Ulcerogenicity (UD): Protocol

Male outbred Wistar rats (100-250 gms) are fasted for 24 hours. After fasting, test compounds are administered orally (in 2 ml/kg of 0.5% hydroxypropyl methylcellulose) and the rats are denied access to food and water for six more hours. The rats are then sacrificed with CO_2 so that the stomachs can be removed, opened along the greater curvature, and evaluated for the presence of gastric ulcers. Results are expressed as the percent of rats with gastric ulcers at a given dose or as the UD_{50} (the dose which causes ulcers in 50% of the rats).

The results of the CFE-2, MFE, and UD assays for each of the noted compounds are shown in the following Table 2.

Table 2

	In Vivo Pharmacology		
Compound	CFE-2[a]	MFE[b]	UD_{50}[c]
Example 4[d]	1.9	3.2	N @ 200

[a] ID_{40} in mg/kg, PO.
[b] ID_{40} in mg/kg, PO.
[c] Dose in mg/kg PO which produces a 50% occurrence of ulcers in rats. N is 0% of rats having ulcers at 200 mg.
[d] Compound tested as its sodium salt.

In addition to the compounds of formula I, the pharmaceutical compositions can also contain other active ingredients, such as cyclooxygenase inhibitors, nonsteroidal antiinflammatory drugs (NSAIDs), peripheral analgesic agents such as zomepirac, diflunisal, and the like. The weight ratio of the compound of

the formula I to the second active ingredient may be varied and will depend upon the effectiv dose of each ingredient. Generally, an effectiv dos of each will be used. Thus, for xampl , wh n a compound of the formula I is combined with an NSAID, th weight ratio of the compound of the formula I to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

Combinations of a compound of the formula I and other active ingredients will generally be in the aforementioned ratios.

NSAIDs can be characterized into five groups:

(1) the propionic acid derivatives;

(2) the acetic acid derivatives;

(3) the fenamic acid derivatives;

(4) the biphenylcarboxylic acid derivatives; and

(5) the oxicams or a pharmaceutically acceptable salt thereof.

The propionic acid derivatives which may be used comprise: ibuprofen, ibuprufen aluminum, indoprofen, ketoprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofen, fluprofen, and bucloxic acid. Structurally related propionic acid derivatives having similar analgesic and antiinflammatory properties are also intended to be included in this group.

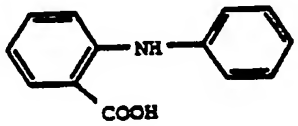
Thus, "propionic acid derivatives' as defined herein are nonnarcotic analgesics/nonsteroidal antiinflammatory drugs having a free $-CH(CH_3)COOH$ or $-CH_2CH_2COOH$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g., $-CH(CH_3)COO^-NA^+$ or $-CH_2CH_2COO^-Na^+$), typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring system.

The acetic acid derivatives which may be used comprise: indomethacin, which is a preferred NSAID, sulindac, tolmetin, zomepirac, diclofenac, fenclofenac, alclofenac, ibufenac, isoxepac, furofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, and fenclozic acid. Structurally related acetic acid derivatives having similar analgesic and antiinflammatory properties are also intended to be encompassed by this group.

Thus, "acetic acid derivatives" as defined herein are nonnarcotic analgesics/nonsteroidal antiinflammatory drugs having a free $-CH_2COOH$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g. $-CH_2CO^- Na^+$), typically attached directly to a ring system, preferably to an aromatic or heteroaromatic ring system.

The fenamic acid derivatives which may be used comprise: mefanamic acid, meclofenamic acid, flufenamic acid, niflumic acid, and tolfenamic acid. Structurally related fenamic acid derivatives having similar analgesic and antiinflammatory properties are also intended to be encompassed by this group.

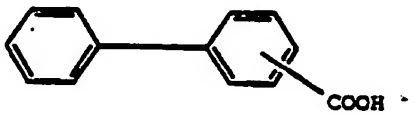
Thus, "fenamic acid derivatives" as defined herein are nonnarcotic analgesics/nonsteroidal antiinflammatory drugs which contain the basic structure:



which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., $-COO^-Na^+$.

The biphenylcarboxylic acid derivatives which can be used comprise: diflunisal and flufenisal. Structurally related biphenylcarboxylic acid derivatives having similar analgesic and antiinflammatory properties are also intended to be encompassed by this group.

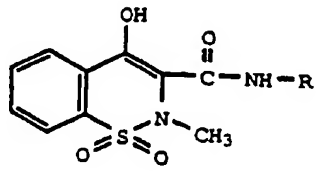
Thus, "biphenylcarboxylic acid derivatives" as defined herein are nonnarcotic analgesics/nonsteroidal antiinflammatory drugs which contain the basic structure:



which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., -COO-Na^+.

The oxicams which can be used in the present invention comprise: piroxicam, sudoxicam, isoxicam, and 4-hydroxyl-1,2-benzothiazine 1,1-dioxide 4-(N-phenyl)-carboxamide. Structurally related oxicams having similar analgesic and antiinflammatory properties are also intended to be encompassed by this group.

Thus, "oxicams" as defined herein are nonnarcotic analgesics/nonsteroidal antiinflammatory drugs which have the general formula:



wherein R is an aryl or heteroaryl ring system.

The following NSAIDs may also be used:

acemetacin, alminoprofen, amfenac sodium, aminoprofen, anitrazafen, antrafenine, auranofin, bendazac lysinate, benzydamine, beprozin, broperamole, bufezolac, carprofen, cinmetacin, ciproquazone, clidanac, cloximate, dazidamine, deboxamet, delmetacin, detomidine, dexindoprofen, diacerein, di-fisalamine, difenpyramide, emorfazone, enfenamic acid, enolicam, epirizole, etersalate, etodolac, etofenamate, fanetizole mesylate, fenclofenac, fenclorac, fendosal, fenflumizole, fentiazac, feprazone, floctafenine, flunixin, flunoxaprofen, fluproquazone, fopirtoline, fosfosal, furcloprofen, furofenac, glucametacin, guaimesal, ibuproxam, isofezolac, isonixim, isoprofen, isoxepac, isoxicam, lefetamine HCl, leflunomide, lofemizole, lonazolac calcium, lotifazole, loxoprofen, lysin, clonixinate, meclofenamate sodium, meseclazone, microprofen, nabumetone, nictindole, nimesulide, orpanoxin, oxametacin, oxapadol, oxaprozin, perisoxal citrate, pimeprofen, pimetacin, piproxen, pirazolac, pirfenidone, pirprofen, pranoprofen, proglumetacin maleate, proquazone, pyridoxiprofen, sudoxicam, suprofen, talmetacin, talniflumate, tenoxicam, thiazolinobutazone, thielavin B, tiaprofenic acid, tiaramide HCl, tiflamizole, timegadine, tioxaprofen, tolfenamic acid, tolpadol, tryptamid, ufenamate, and zidometacin.

Finally, NSAIDs which may also be used include the salicylates, specifically aspirin, and the phenylbutazones, and pharmaceutically acceptable salts thereof.

Pharmaceutical compositions comprising the formula I compounds may also contain as the second active ingredient, antihistaminic agents such as benadryl, dramamine, histadyl, phenergan, and the like. Alternatively, they may include prostaglandin antagonists such as those disclosed in European Patent Application 11,067 or thromboxane antagonists such as those disclosed in U.S. 4,237,160. They may also contain histidine decarboxylase inhibitors such as α-fluoromethylhistidine, described in U.S. 4,325,961. The compounds of the formula I may also be advantageously combined with an H_1 or H_2-receptor antagonist, such as for instance cimetidine, ranitidine, terfenadine, famotidine, temelastine, acrivastine, loratadine, cetrizine, tazifylline, azelastine, aminothiadiazoles disclosed in EP 81102976.8 and like compounds, such as those disclosed in U.S. Patent Nos. 4,283,408; 4,362,736; 4,394,508, and European Patent Application No. 40,696. The pharmaceutical compositions may also contain a K^+/H^+ ATPase inhibitor such as omeprazole, disclosed in U.S. Patent 4,255,431, and the like. Each of the references referred to in this paragraph is hereby incorporated herein by reference.

The compounds of the formula I and their salts are prepared generally by the following processes and constitute a further aspect of the present invention.

In the following processes Ar =